Cytokine release syndrome (CRS) following treatment with tebentafusp, a novel bispecific TCR–anti-CD3 directed against gp100, in patients with advanced melanoma

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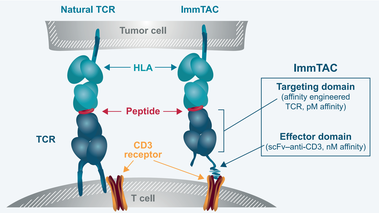
Background

- ImmTAC® (immune-mobilizing monoclonal T cell receptor [TCR] against cancer) molecules are bispecific fusion proteins with an effector end consisting of an affinity-enhanced TCR, which is engineered to target intracellular antigens presented as peptide–human leukocyte antigen (HLA) complexes, and an anti-CD3 single-chain variable fragment (scFv) effector end (**Figure 1**)
- Tebentafusp (IMCgp100) is designed to be a first-in-class investigational ImmTAC® molecule capable of engaging, redirecting, and activating polyclonal CD3+ T cells against the melanocyte-associated antigen gp100, resulting in lysis of gp100+ target cells
- In early clinical studies, tebentafusp showed monotherapy activity in advanced melanoma with mechanism of action–related changes in peripheral cytokines and circulating T cells[1]
- CRS recognition and management is based on non-specific clinical signs including fever, hypotension, and hypoxia

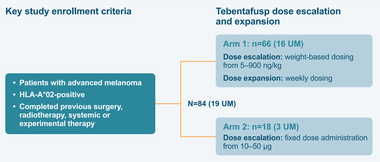
Figure 1. ImmTAC® molecules have been designed to mimic the immune synapse formed by a natural T cell–tumor cell interaction



Methods

- IMCgp100-01 was a multi-center, Phase I/II, open-label, dose-finding study to assess the safety, tolerability, and efficacy of tebentafusp in patients with advanced malignant melanoma (NCT01211262)
- 84 HLA-A*02-positive patients with advanced melanoma received tebentafusp
- The study assessed a weekly and daily dosing regimen for tebentafusp (**Figure 2**)
- Per protocol, patients did not receive corticosteroids as CRS prophylaxis
- AEs, SAEs, vital signs, and concomitant medications reported by investigators were evaluated by Immunocore (Sponsor) medical review post hoc to identify episodes of CRS based on criteria in Lee et al[2]
  - Each distinct CRS episode identified was typically composed of more than one AE and/or abnormal vital sign after a given dose (e.g., fever, fatigue, temperature ≥38°C, hypotension, BP <90/60)
- Circulating cytokines interferon γ (IFNγ), interleukin-6 (IL-6), IL-10 and tumor necrosis factor α (TNFα) were measured using Meso Scale Discovery (n=25) or Luminex (n=45) platform

Figure 2. Study Design



Arm 2 received tebentafusp once daily x 4 days every 3 weeks
UM: uveal melanoma

Results

Table 1. Baseline demographics and characteristics

Characteristic		Total (N=84)
Gender, n (%)	Male	54 (64)
	Female	30 (36)
Age, mean (range), years		58.7 (25–78)
Melanoma type, n (%)	Cutaneous	61 (73)
	Uveal	19 (23)
	Other*	4 (5)
Number of prior systemic treatments, median (range)		1 (0–6)
Prior systemic therapy, n (%)†	Any	59 (70)
	Chemotherapy	29 (35)
	Immunotherapy‡	42 (50)
	Anti-PD-X§	21 (25)
	Other targeted therapy (± chemotherapy)	24 (29)

*Other melanoma types included: acral, unknown primary, lentiginous (vulval), mucosal (rectal); †To be eligible for the trial, patients must have completed previous surgery (other than resection of skin metastases), radiotherapy, chemotherapy, immunotherapy or experimental therapy>4 weeks previously. The 25 patients who did not receive prior systemic therapy were previously treated with either surgery, radiotherapy or local chemotherapy; ‡Immunotherapy includes anti-PD-X, anti-CTLA-4, combination, and other; §Anti-PD-X includes anti-PD-1 and anti-PD-L1

CTLA-4: cytotoxic T-lymphocyte antigen 4; PD-1: programmed death-1; PD-L1: programmed death-ligand 1; PD-X: treatment with anti-PD-1 or anti-PD-L1 therapy

Table 2. Lee CRS grading criteria[2]

Grade	Symptoms
1	Mild symptoms that are not life-threatening and require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, and malaise)
2	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% • Hypotension responsive to fluids or one low-dose vasopressor • Grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention • Oxygen requirement ≥40% • Hypotension requiring high-dose or multiple vasopressors • Grade 3 organ toxicity • Grade 4 transaminitis
4	Life-threatening symptoms • Requirement for ventilator support • Grade 4 organ toxicity (excluding transaminitis)
5	Death

- Treatment-related AEs (any grade) per investigator that were also cytokine-mediated per Lee criteria[2] were mostly mild to moderate (**Table 3**)
- 57% of patients had fever, the hallmark of CRS
- Investigators separately reported episodes of CRS in two patients

Table 3. Select cytokine-mediated treatment-related AEs

Treatment-related AE	Total (N=84)	
	All grades n (%)	≥Grade3 n (%)
Pyrexia	48 (57)	4 (5)
Fatigue	35 (42)	0 (0)
Nausea	34 (40)	0 (0)
Hypotension	27 (32)	6 (7)
Headache	19 (23)	0 (0)
Hypoxia	3 (4)	0 (0)
CRS	2 (2)	1 (1)

- 50 of 84 patients (60%) were determined by Sponsor to have experienced any grade CRS (**Table 4**)

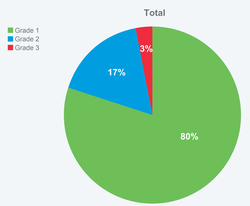
Table 4. Highest post-hoc CRS grade by patient

(N=84)	N (%)	Most common AE
No CRS	34 (40.4%)	Not applicable
Grade 1	35 (41.7%)	Pyrexia, nausea, fatigue
Grade 2	12 (14.3%)	Pyrexia, hypotension, nausea
Grade 3	3 (3.6%)	Pyrexia, hypotension, hypoxia

Patients continued tebentafusp treatment despite CRS, with only two patients discontinuing due to CRS

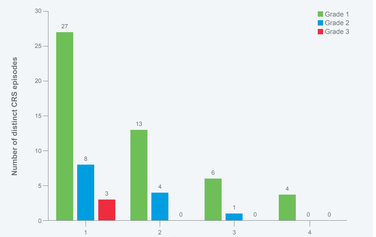
- Based on post-hoc analysis, 100 distinct CRS episodes occurred in 50 of 84 patients
- CRS episodes were mostly mild to moderate in grade (97% Grade 1–2) (**Figure 3**)

Figure 3. CRS episodes (all grades)



- CRS episodes most commonly occurred after the first dose, with decreased frequency and severity after subsequent doses (**Figure 4**)

Figure 4. Number of distinct CRS episodes after first 4 doses: Arm 1



Patients could experience a distinct CRS episode as identified by Sponsor after more than 1 dose
All 3 episodes of Grade 3 CRS occurred after the first tebentafusp dose
No episodes of ≥Grade 2 CRS occurred after the third dose in Arm 1

- Increased body temperature began within a few hours of tebentafusp administration in patients identified as experiencing CRS following dose 1 (**Figure 5**)

Figure 5. Mean change from baseline body temperature over time following dose 1

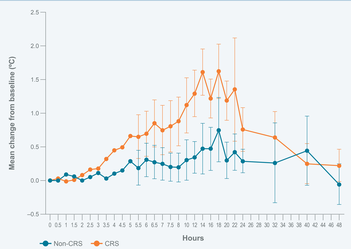
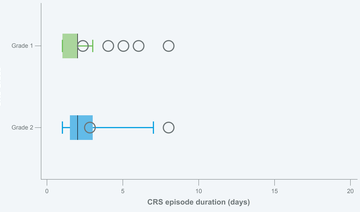


Table 5. The predictive value of a 1°C increase in body temperature at various timepoints for ≥Grade 2 CRS

Timepoint (Hours post tebentafusp administration)	Sensitivity (True Positive Rate)	1-Sensitivity (False Negative Rate)	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Overall Accuracy
8	8/11 = 73%	3/11 = 27%	8/23 = 35%	40/43 = 93%	48/66 = 73%
10	8/11 = 73%	3/11 = 27%	8/28 = 29%	35/38 = 92%	43/66 = 65%
12	8/11 = 73%	3/11 = 27%	8/32 = 25%	31/34 = 91%	39/66 = 59%

- CRS episodes typically of short duration (**Figure 6**)

Figure 6. CRS duration by grade



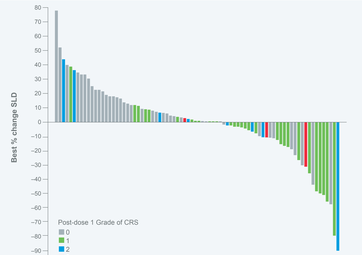
Grade 3 CRS episodes were 3, 4, and 16 days in duration; The 16 day episode occurred in a patient with mucosal melanoma, extensive pulmonary metastases, COPD, and emphysema who developed 1 day of fever and hypotension the day of tebentafusp administration as well as respiratory distress, which resolved after 16 days.
One grade 1 CRS episode not captured in figure 6 had fever of 22 days reported duration.
Events of nausea, fatigue, headache, myalgia, malaise, and dehydration could be ongoing to consider an episode resolved.

- Most CRS episodes conservatively managed
- Grade 2 and 3 CRS episodes treated with intravenous fluid (IVF), corticosteroids, and supplemental oxygen as needed (**Table 6**)

Table 6. Treatment medication in patients experiencing CRS

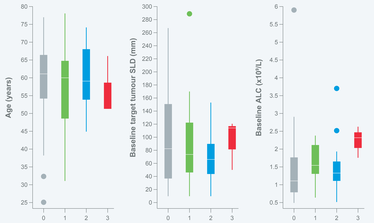
Treatment received	Grade 1	Grade 2	Grade 3	Grade 4	Total
Tocilizumab	0	0	0	0	0
Vasopressors	0	0	2	0	2
IV steroids	3	5	2	0	10
Oxygen	0	2	3	0	5
IVF	0	16	3	0	19

Figure 7. Patients experiencing CRS following the first tebentafusp dose showed the greatest reductions in tumor size



Best percentage reduction in target tumor SLD; bar per patient, colored by occurrence and (highest) grade of CRS following the first dose of tebentafusp (n=82).
SLD: sum of the longest diameters.

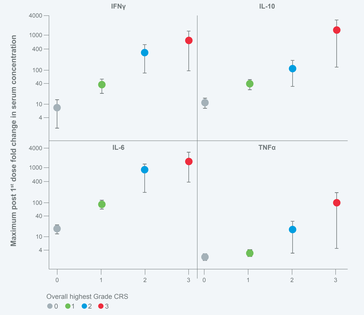
Figure 8. Occurrence of any Grade CRS not associated with age, absolute lymphocyte count, or disease burden (SLD of target lesions) at baseline



Patients grouped by overall (highest) grade of CRS, in terms of baseline a) age, b) SLD of target tumors and c) absolute lymphocyte count. Box plots represents first and third quartile with median indicated; whiskers represent upper and lower adjacent values.
ALC: absolute lymphocyte count.

- Consistent with the hypothesized mode of action (supported by preclinical data), transient increases in peripheral cytokines occurred within hours of tebentafusp administration, and tended to be greater in patients with higher grade CRS (**Figure 9**)

Figure 9. Patients experiencing CRS following tebentafusp dose tended to show greater cytokine response



Maximum fold increase from baseline in serum levels of IFNγ, IL-10, IL-6, and TNFα measured across post-first-dose-sampling time points between 4h and 48h for 70 patients. Patients grouped by overall (highest) grade of CRS. Data points represent mean ± SEM.

Conclusions

- Low incidence of severe CRS as determined by Sponsor review, using Lee et al criteria[2]
- Without mandatory corticosteroid pretreatment, CRS generally low grade, reversible with standard management (including IVF and short course corticosteroids), decreased in frequency and severity after initial doses, and infrequently led to discontinuation
- Most frequent CRS AEs: mild-to-moderate fever, fatigue, nausea, hypotension, headache
- Patients with less than 1°C increase in body temperature by 8 hours less likely to develop subsequent moderate or higher CRS
- CRS after first dose appears associated with reduction in tumor size
- Higher grade CRS appears associated with key serum cytokines

References

1. Middleton MR, Steven NM, Evans JT, et al. Relationship between clinical efficacy and AEs of IMCgp100, a novel bispecific TCR–anti-CD3, in patients with advanced melanoma. Presented at ASCO 2019; Abstract 9523
2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood* 2014;124:188–195

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